DOCKET NO.: GLIS-0144 PATENT

Application No.: 10/080,074

Office Action Dated: August 25, 2004

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (Currently Amended). A compound having the structure (1):

$$\begin{array}{c|c}
R^{2} & R^{27} \\
R^{27} & R^{27} \\
R^{27} & R^{27} \\
R^{27} & R^{27}
\end{array}$$
(1)

and tautomers, solvates and salts thereof, wherein

R¹ is an oligonucleotide, a protecting group, a linker or -H;

 R^2 is $A(Z)_{X1}$, wherein A is a spacer and Z independently is a label bonding group optionally bonded to a detectable label, but R^2 is not [amine] <u>NH2</u>, protected [amine] <u>NH2</u>, nitro or cyano;

 R^{27} is independently -CH=, -N=, -C(C₁-C₈ alkyl)= or -C(halogen)=, but no adjacent R^{27} are both -N=, or two adjacent R^{27} are taken together to form a ring having the structure,

Application No.: 10/080,074

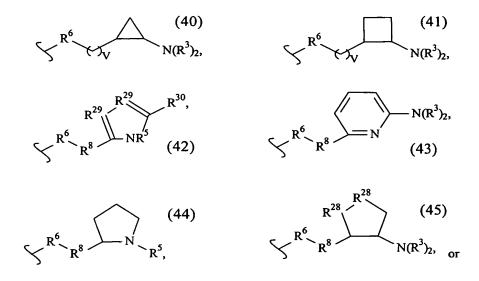
Office Action Dated: August 25, 2004

where R^a is independently -CH=, -N=, -C(C_1 - C_8 alkyl)= or -C(halogen)=, but no adjacent R^a are both -N=;

$$R^{34}$$
 is -O-, -S- or -N(CH₃)-; and . and X^1 is 1, 2 or 3.

2 (Original). The compound of claim 1 wherein R^2 is $-R^{2C}-R^{2D}$, wherein R^{2C} is a short spacer chain and R^{2D} is a hydrogen bond donor moiety or a moiety having a net positive charge of at least about +0.5 at pH 6-8 in aqueous solutions.

3. (Currently Amended) The compound of claim 1, wherein R^2 is $[-R^6-(CH_2)_tNR^5C(NR^5)(NR^3)_2,] - \frac{R^6-(CH_2)_tNR^5C(NR^5)N(R^3)_2}{-R^6-(R^7)_v-N(R^3)_2}, -R^6-(CH_2)_t-N(R^3)_2, -(CH_2)_{t-2}-O-(CH_2)_t-N(R_3)_2,$



Page 3 of 22

DOCKET NO.: GLIS-0144 Application No.: 10/080,074

Office Action Dated: August 25, 2004

$$\begin{array}{c|c}
R^{28} - R^{28} & (46) \\
& & \\
& & \\
N(R^3)_{2}, \\
\end{array}$$

 R^3 is independently -H, -CH₃, -CH₂CH₃, -(CH₂)_w-N(R^{33})₂ or a protecting group, or both R^3 together are a protecting group, or when R^2 is $[-R^6-(CH_2)_t-N(R^3)_2,]$ - $R^6-(CH_2)_t-N(R^{33})_2$ one R^3 is -H, -CH₃, -CH₂CH₃, a protecting group or -(CH₂)_w-N(R^{33})₂ and the other R^3 is -H, -CH₃, -CH₂CH₃, -(CH₂)_w-N(R^{33})₂, -CH(N(R^{33})₂)-N(R^{33})₂,

$$\begin{array}{c}
\mathbb{R}^{35} \\
\mathbb{N} \\
\mathbb{N}
\end{array}$$
or
$$\mathbb{N} - \mathbb{R}^{36} \\
\mathbb{N} \\
\mathbb{N}$$

R⁵ is independently H or a protecting group;

R⁶ is independently -S-, -NR⁵-, -O- or -CH₂-;

 R^7 is independently linear alkyl having 1, 2, 3 or 4 carbon atoms optionally substituted with one -CH=CH-, -C=C- or -CH₂-O-CH₂- moiety, or R^7 is cyclic alkyl having 3, 4 or 5 carbon atoms, wherein one of the linear alkyl carbon atoms is optionally substituted with a single -CH₃, -CN, =O, -OH or protected hydroxyl, provided that the carbon atoms in any -CH=CH- or -CH₂-O-CH₂- moiety

DOCKET NO.: GLIS-0144 Application No.: 10/080,074

Office Action Dated: August 25, 2004

are not substituted with =0, -OH or protected hydroxyl;

R⁸ is linear alkylene having 1 or 2 carbon atoms wherein one alkylene carbon atom is optionally substituted with a single -CH₃, -CN, =O, -OH or protected hydroxyl, or R⁸ is absent;

 R^{28} is independently -CH₂-, -CH(CH₃)-, -CH(OCH₃)-, -CH(OR⁵)- or -O-, but both are not -O-;

 R^{29} is independently -N-, -N(CH₃)-, -CH-, -C(CH₃)-, but both are not -N(CH₃)-;

 R^{30} is -H or -N(R^3)₂;

R³¹ is the side chain of an amino acid;

R³³ is independently -H, -CH₃, -CH₂CH₃ or a protecting group;

R³⁵ is H, C₁-C₄ alkyl or a protecting group;

R³⁶ is H, -CH₃, -CH₂CH₃, a protecting group or an optionally protected monosaccharide;

t is 1, 2, 3 or 4, but when R⁶ is -O-, -S- or -NR⁵-, t is 2, 3 or 4;

v is independently 0, 1 or 2; and

w is independently 1 or 2.

4. (Previously Presented) The compound of claim 3 wherein R^2 is $-CH_2-(CH_2)_tN(R^3)_2$, $-NR^5-(CH_2)_tN(R^3)_2$, $-S-(CH_2)_tN(R^3)_2$, $-O-(CH_2)_tN(R^3)_2$, $[-O-(CH_2)_tNR^5C(NR^5)(NR^3)_2]$, $-O-(CH_2)_tNR^5C(NR^5)N(R^3)_2$, $-(CH_2)_{1-2}-O-(CH_2)_tN(R^3)_2$, $-R^6-CH_2-CHR^{31}-N(R^3)_2$, $-R^6-(R^7)_v-N(R^3)_2$, $-R^6-(CH_2)_t-NR^5C(NR^5)(NR^3)_2$, $-R^6-(CH_2)_t-NR^5C(NR^5)N(R^3)_2$, or $[-CH_2-(CH_2)_tNR^5C(NR^5)N(R^3)_2$.

DOCKET NO.: GLIS-0144 Application No.: 10/080,074

Office Action Dated: August 25, 2004

5 (Original). The compound of claim 4 wherein t is 2.

6 (Original). The compound of claim 5 wherein R^3 independently is -H, -CH₃, -C₂H₅ or a protecting group.

7 (Original). The compound of claim 6 wherein R² is -O-(CH₂)₂-NH₂, -O-(CH₂)₃-NH₂, -O-(CH₂)₂-N(CH₃)₂, -O-(CH₂)₃-N(CH₃)₂, -O-(CH₂)₂-NHCH₃, -O-(CH₂)₃-NHCH₃, -O-CH₂-CH(CH₃)-NH₂, -CH₂-O-(CH₂)₂-NH₂, -CH₂-O-(CH₂)₃-NH₂ or -(CH₂)₂-O-(CH₂)₂-NH₂.

8 (Original). The compound of claim 3 wherein t is 2 or 3.

9 (Original). The compound of claim 1 wherein R¹ comprises -H, an optionally protected monosaccharide, hydroxyl, phosphate or hydrogen phosphonate.

10 (Original). The compound of claim 1 wherein R¹ is optionally protected 2'-deoxy-R²¹-substituted ribose, 2'-deoxyribose or ribose, wherein R²¹ is H, -OH, halogen or a moiety that enhances the nuclease stability of an oligonucleotide containing the optionally protected 2'-deoxy-R²¹-substituted ribose, 2'-deoxyribose or ribose.

Office Action Dated: August 25, 2004

11 (Currently Amended). The compound of claim 1 having the structure designated by the numbers selected from the group consisting of (104), (105), (133), (134), (111), (112), (113), (115)] (114), (135), (136), (137), (138), (139), (120), (121), (121A), (143), (122), (123), (125), or (126):

-continued

Page 7 of 23

DOCKET NO.: GLIS-0144 Application No.: 10/080,074

Office Action Dated: August 25, 2004

-continued

$$R^{37}$$

$$R^{30}$$

$$R^{21}$$

$$R^{21}$$

CBZNH(
$$R^{50}$$
)_YCH₂CH₂ R^{27} R^{27}

$$H_2N(R^{50})_YCH_2CH_2$$
 R^{27}
 R^{27}
 R^{27}
 R^{27}
 R^{27}
 R^{27}
 R^{27}

$$\begin{array}{c|c}
R^{52} & & \\
HN & R^{27} \\
R^{27} & & \\
R^{27} & & \\
R^{34} & & \\
\end{array}$$

$$H_2NR^{59}$$
 R^{27}
 R^{27}
 R^{27}
 R^{27}
 R^{27}
 R^{27}

Page 8 of 23

(126)

DOCKET NO.: GLIS-0144 Application No.: 10/080,074

Office Action Dated: August 25, 2004

-continued (123)
$$H_2NR^{52} \longrightarrow R^{27}$$

$$H \longrightarrow R^{37}$$

$$R^{27}$$

$$R^{27}$$

$$R^{27}$$

$$R^{27}$$

$$R^{27}$$

$$R^{21}$$

$$R^{21}$$

$$R^{21}$$

$$R^{21}$$

$$R^{21}$$

$$R^{22}$$

$$R^{21}$$

$$R^{22}$$

$$R^{23}$$

$$R^{24}$$

$$R^{27}$$

$$R^{$$

wherein

 R^1 is an optionally protected monosaccharide; R^{2A} is -OH; R^5 is independently -H or a protecting group; R^6 is -O-, -S-, -NH- or -CH2-, R^{21} is H, -OH, halogen or a moiety that enhances the nuclease stability of an oligonucleotide; R^{24} is a halogen; R^{27} is independently -CH=, -N=, -C(C_1 - C_8 alkyl)= or [-C(halogen =] -C(halogen)=, but no adjacent R^{27} are both -N=, or two adjacent R^{27} are taken together to form a ring having the structure,

Office Action Dated: August 25, 2004

where

R^a is independently -CH=, -N=, -C(C_{1.8} alkyl)= or -C(halogen)=, but no adjacent R^a are both -N=; R³⁴ is -O-, -S- or -N(CH₃)-; R³⁷ is -O-, -CH₂- or -CF₂-; R⁴⁷ is -O- or -S-; R⁵⁰ is -CH₂-, -C(O)-, -(CH₂)-O-(CH₂)₂-, -(CH₂)₂-, -(CH₂)₂-, -(CH₂)₂-, -CH(N(R⁵)₂)-, -CH (COOR⁵)- or -C(CH₃)-, -C(C₂C₅)- but adjacent moieties are not C(O); R⁵² is -(CHR^{52A})-(R^{52B})-CHR^{52A}-, - CHR^{52A}-, -CHR^{52A}-, -CH

12 (Original). The compound of claim 1 wherein R¹ is an oligo-nucleotide having the structure (2):

wherein D is -OH, protected -OH, an oligonucleotide coupling group or a solid support;

DOCKET NO.: GLIS-0144 PATENT

Application No.: 10/080,074

Office Action Dated: August 25, 2004

D¹ is an oligonucleotide coupling group, -OH, protected -OH or a solid support, wherein D¹ is bonded to one 2' or 3' position in the oligonucleotide of structure (2) and the adjacent 2' or 3' position in structure (2) is substituted with R²¹, provided that D and D¹ are not both an oligonucleoide coupling group or they are not both a solid support; R⁴ is independently a phosphodiester linkage or a phosphodiester substitute linkage, wherein R⁴ is bonded to one 2' or 3' position in the structure (2) oligonucleotide and the adjacent 2' or 3' position in structure (2) is substituted with R²¹;
R²¹ is independently -H, -OH, halogen or a moiety that enhances the oligonucleotide against nuclease cleavage; R³² is independently -O-, -CH₂-, -CF₂-; n is an integer from 0 to 98; and B independently is a purine or pyrimidine base or a protected derivative thereof, provided that at least one B is a base of structure (3)

13 (Currently Amended). The compound of claim 12 wherein R^4 is independently 3'-O-P(S)(S)-O-5', 3'-O-P(S)(O)-O-5', wherein S^{38} independently is $S^{38}-O^{38$

DOCKET NO.: GLIS-0144

Application No.: 10/080,074

Office Action Dated: August 25, 2004

PATENT

 C_1 - C_{12} alkyl optionally substituted with one, or two -O-, -C(O)-, -OC(O)-, -C(O)O-, -OR⁴², -SR⁴³, -C(O)NR³⁹-, -C(O)N(R⁴¹)₂, -NR⁴¹-, -N(R⁴¹)₂, halo, -CN, or -NO₂ moieties, or both R⁴⁰ together with the nitrogen atom to which they are attached form

or both R⁴⁰ together are a protecting group;

 R^{41} independently is hydrogen, a protecting group, alkyl (C_1 - C_4 or both R^{41} together are a protecting group; R^{42} is hydrogen or a protecting group; R^{43} is C_{1-6} alkyl or a protecting group; and R^{45} is - H, a counter ion or

Office Action Dated: August 25, 2004

R⁴⁶ is alkyl containing 1-8 carbon atoms.]

14. (Currently Amended) The compound of claim 12, wherein R^2 is $[-R^6-(CH_2)_tNR^5C(NR^5)(NR^3)_2, -R^6-(CH_2)_tNR^5C(NR^5)N(R^3)_2, -R^6-CH_2-CHR^{31}-N(R^3)_2, -R^6-(R^7)_v-N(R^3)_2, -R^6-(CH_2)_t-N(R^3)_2, -(CH_2)_t-O-(CH_2)_t-N(R_3)_2,$

$$R^{29}$$
 R^{29}
 R^{30}
 R^{30}
 R^{6}
 R^{8}
 R^{8}
 R^{8}
 R^{8}
 R^{10}
 R^{10}

Office Action Dated: August 25, 2004

$$\begin{array}{c|c}
R^{28} - R^{28} & (46) \\
R^{6} & & \\
N(R^{3})_{2},
\end{array}$$

 R^3 is independently -H, -CH₃, -CH₂CH₃, -(CH₂)_w-N(R^{33})₂ or a protecting group, or both R^3 together are a protecting group, or when R^2 is $[-R^6-(CH_2)_t-N(R^3)_2]$ - $R^6-(CH_2)_t-N(R^{33})_2$, one R^3 is -H, -CH₂CH₃, a protecting group or -(CH₂)_w-N(R^{33})₂ and the other R^3 is -H, -CH₃, -CH₂CH₃, -(CH₂)_w-N(R^{33})₂, -CH(N(R^{33})₂)-N(R^{33})₃,

$$\begin{array}{c}
\mathbb{R}^{35} \\
\mathbb{N}
\end{array}$$
or
 $\mathbb{N}-\mathbb{R}^{36}$

R⁵ is independently H or a protecting group;

R⁶ is independently -S-, -NR⁵-, -O- or -CH₂-;

 R^7 is independently linear alkyl having 1, 2, 3 or 4 carbon atoms optionally substituted with one -CH=CH-, -C=C- or -CH₂-O-CH₂- moiety, or R^7 is cyclic alkyl having 3, 4 or 5 carbon atoms, wherein one of the linear alkyl carbon atoms is optionally substituted with a single -CH₃, -CN, =O, -OH or protected hydroxyl, provided that the carbon atoms in any -CH=CH- or -CH₂-O-CH₂- moiety

DOCKET NO.: GLIS-0144
PATENT

Application No.: 10/080,074

Office Action Dated: August 25, 2004

are not substituted with =O, -OH or protected hydroxyl;

R⁸ is linear alkylene having 1 or 2 carbon atoms wherein one alkylene carbon atom is optionally substituted with a single -CH₃, -CN, =O, -OH or protected hydroxyl, or R⁸ is absent;

R²⁸ is independently -CH₂-, -CH(CH₃)-, -CH(OCH₃)-, -CH(OR⁵)- or -O-, but both are not -O-;

R²⁹ is independently -N-, -N(CH₃)-, -CH-, -C(CH₃)-, but both are not -N(CH₃)-;

 R^{30} is -H or -N(R^{3})₂;

R³¹ is the side chain of an amino acid;

R³³ is independently -H, -CH₃, -CH₂CH₃ or a protecting group;

R³⁵ is H, C₁-C₄ alkyl or a protecting group;

R³⁶ is H, -CH₃, -CH₂CH₃, a protecting group or an optionally protected monosaccharide;

t is 1, 2, 3 or 4, but when R⁶ is -O-, -S- or -NR⁵-, t is 2, 3 or 4;

v is independently 0, 1 or 2; and

w is independently 1 or 2.

15. (Previously Presented) The compound of claim 14 wherein R² is $-CH_2-(CH_2)_tN(R^3)_2$, $-NR^5-(CH_2)_tN(R^3)_2$, $-S-(CH_2)_tN(R^3)_2$, $-O-(CH_2)_tN(R^3)_2$, $[-O-(CH_2)_tNR^5C(NR^5)(NR^3)_2]$, $[-O-(CH_2)_tNR^5C(NR^5)N(R^3)_2]$, $-O-(CH_2)_tNR^5C(NR^5)N(R^3)_2$, $-(CH_2)_{1-2}-O-(CH_2)_tN(R^3)_2$, $-R^6-CH_2-CHR^{31}-N(R^3)_2$, $-R^6-(R^7)_v-N(R^3)_2$, $[-R^6-(CH_2)_t-NR^5C(NR^5)(NR^3)_2]$, $-R^6-(CH_2)_t-NR^5C(NR^5)N(R^3)_2$, or $[-CH_2-(CH_2)_tNR^5C(NR^5)(NR^3)_2]$, $-CH_2-(CH_2)_tNR^5C(NR^5)N(R^3)_2$.

16 (Original). The compound of claim 15 wherein t is 2 or 3.

DOCKET NO.: GLIS-0144 Application No.: 10/080,074

Office Action Dated: August 25, 2004

17 (Original). The compound of claim 16 wherein R³ independently is -H, -CH₃, -C₂H₅ or a protecting group.

18 (Original). The compound of claim 17 wherein R² is -O-(CH₂)₂-NH₂, -O-(CH₂)₃-NH₂, -O-(CH₂)₂-N(CH₃)₂, -O-(CH₂)₃-N(CH₃)₂, -O-(CH₂)₂-NHCH₃, -O-(CH₂)₃-NHCH₃, -O-CH₂-CH(CH₃)-NH₂, -CH₂-O-(CH₂)₂-NH₂, -CH₂-O-(CH₂)₃-NH₂ or -(CH₂)₂-O-(CH₂)₂-NH₂.

19 (Currently Amended). The compound of claim 12 wherein R^{21} is independently -H, -OH, halogen, protected hydroxyl, -O-methyl, O-ethyl, O-n-propyl, O-allyl, -O- $(CH_2)_2$ -OH, -O- $(CH_2)_3$ -OH, -O- $(CH_2)_2$ -F, -O- $(CH_2)_s$ -R⁶⁵, -O- $(CH_2)_2$ -[O- $(CH_2)_2$]_r-R⁶⁵, [-O- $(CH_2)_r$ -O- $(CH_2)_r$ -O- $(CH_2)_r$ -O- $(CH_2)_r$ -O- $(CH_2)_r$ -O- $(CH_2)_r$ -NH-methyl, -NH-ethyl, -NH-n-propyl, -NH- $(CH_2)_2$ -OH, -NH- $(CH_2)_3$ -OH, -NH- $(CH_2)_s$ -R⁶⁵, -S-methyl, -S-ethyl, -S-n-propyl, -S-allyl, -S- $(CH_2)_2$ -OH, -S- $(CH_2)_3$ -OH, -S- $(CH_2)_2$ -F, -S- $(CH_2)_s$ -R⁶⁵, or -S- $(CH_2)_2$ -[O- $(CH_2)_2$]_r-R⁶⁵, wherein:

R⁶⁵ is -H, -F, -OH, -OCH₃, -NH₂, -SH, protected hydroxyl, protected amino or protected thiol;

r is 1, 2, 3, or 4; and

s is 2, 3, 4, 5, 6, 7 or 8.

20 (Original). The compound of claim 19 wherein R²¹ is independently -H, -OH, -F, protected hydroxyl, -OCH₃, -O-CH₂CH₃, -O-CH₂CH₂OH, -O-CH₂CH₂F, -O-CH₂CH₂CH₃, -O-CH₂CH₂CH₂OH, -O-CH₂CH₂CH₂CH₃, or -O-CH₂CH₂CH₂OH, -O-CH₂CH₂CH₃.

DOCKET NO.: GLIS-0144

PATENT

Application No.: 10/080,074

Office Action Dated: August 25, 2004

21 (Original). The compound of claim 12 wherein B independently are selected from the group consisting of a base of structure (3), guanosine, adenine, thymine, uracil, cytosine, 5-methylcytosine, 5-(1-propynyl)uracil, 5-(1-propynyl)cytosine, 5-(1-butynyl)uracil therefor 5-(1-butynyl)cytosine.

22 (Original). The compound of claim 12 wherein D^1 is H-phosphonate, a methylphosphonamidite, a β -cyanoethylphosphoramidite or phosphoramidite.

23 (Original). A compound having the structure (4):

$$\begin{array}{c|c}
R^{2} & R^{27} \\
R^{27} & R^{27} \\
R^{$$

and tautomers, solvates and salts thereof, wherein

R¹, R² and R²⁷ have the meanings given in claim 1;

R²⁴ is halogen;

 R^{25} is -SH, -OH, =S or =O.

24 (Original). The compound of claim 23 wherein R¹ is -H, or an optionally protected monosaccharide.

Office Action Dated: August 25, 2004

25 (Original). The compound of claim 24 wherein the optionally protected monosaccharide is 2'-deoxy-R²¹-substituted ribose, wherein R²¹ is H, -OH, halogen or a moiety that enhances the nuclease stability of an oligonucleotide containing the optionally protected 2'-deoxy-R²¹-substituted ribose, 2'-deoxyribose or ribose.

26 (Original). The compound of claim 25 wherein R²¹ is -H, -OH, -F, protected hydroxyl, -OCH₃, -O-CH₂CH₃, -O-CH₂CH₂OH, -O-CH₂CH₂CH₂CH₂OH, -O-CH₂CH₂CH₂CH₂OH, -O-CH₂CH₂CH₂CH₂CH₂OH, -O-CH₂CH₂CH₂CH₂O-CH₃.

27 (Original). A compound having the structure (1):

$$R^{2}$$
 R^{27}
 R^{27}

or tautomers, solvates or salts thereof, wherein:

R¹ is a protecting group, an oligonucleotide, a nucleic acid, a polysaccharide, an optionally protected monosaccharide, hydroxyl, phosphate, hydrogen phosphate, halo, azido, protected hydroxyl or -H;

 R^2 is $A(Z)_{X1}$, but R2 is not amine, protected amine, nitro or cyano;

R⁵ independently H or a protecting group;

 R^{27} is, independently, -CH=, -N=, -C(C_1 - C_8 alkyl)= or -C(halogen)=, but no adjacent R^{27}

DOCKET NO.: GLIS-0144

Application No.: 10/080,074

Office Action Dated: August 25, 2004

are both -N=; or two adjacent R²⁷ are taken together to form a ring having the structure:

PATENT

R³⁴ is -O-, -S- or -N(CH₃)-;

 R^a is independently -CH=, -N=, -C(C₁₋₈ alkyl)= or -C(halogen)=, but no adjacent R^a are both -N=;

A is a backbone chain of 2-16 carbon atoms, any 1, 2 or 3 of which are optionally replaced with N, O or S atoms, wherein the backbone chain is optionally substituted independently with 1, 2 or 3 of the following: C_1 - C_8 alkyl, $-OR^5$, =O, $-NO_2$, $-N_3$, $-COOR^5$, $-N(R^5)_2$, or -CN groups, C_1 - C_8 alkyl substituted with -OH, =O, $-NO_2$, $-N_3$, $-COOR^5$, $-N(R^5)_2$, or -CN groups, or any of the foregoing in which $-CH_2$ - is replaced with -O-, -NH- or $-N(C_1$ - C_8 alkyl);

 X^1 is 1, 2 or 3;

Y is H, 2-hydroxypyridine, N-hydroxysuccinimide, p-nitrophenyl, acylimidazole, maleimide, trifluoroacetate, an imido, a sulfonate, an imine 1,2-cyclohexanedione, glyoxal or an alpha-halo ketone; and

Z independently is -NH₂, -CHO, -SH, -CO₂Y, OY.

28 (Original). The compound of claim 27 wherein Z is bonded to a detectable label.

29 (Original). The compound of claim 27 wherein R¹ is an oligonucleotide.

30 (Original). The compound of claim 27 wherein R¹ is an optionally protected monosaccharide.